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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/173,463	10/14/98	BLACK M	240052.429

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EXAMINER	
FRONDA, C	
ART UNIT	**PAPER NUMBER**
1652	8

DATE MAILED: 07/06/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/173,463	Black
Examiner	**Group Art Unit**
Christian L. Fronda	1652

☐ Responsive to communication(s) filed on _____.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 1-60 is/are pending in the application.

Of the above, claim(s) 16-60 is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 1-15 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 7

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Election/Restriction

1. In the **RESPONSE TO RESTRICTION REQUIREMENT** dated June 2, 2000 (paper no.6) applicant elects Group I, claims 1-15. This election has been acknowledged and claims 1-15 have been examined.

Claim Rejections - 35 U.S.C. § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. Claims 1-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Munir *et al.* in view of Graham *et al.*, Kit *et al.*, Drake *et al.*, Waldman *et al.*, Munch-Petersen *et al.*, Balasubramaniam *et al.*, Brown *et al.*, and Donarian *et al.*

Munir *et al.* teach methods to randomly mutate DNA encoding Herpes Simplex Virus Type 1 thymidine kinase (HSV-1 tk) (see entire publication). Munir *et al.* do not teach the isolated nucleic acid of claims 1-11. Graham *et al.* teach the gene encoding Herpes Simplex Virus Type 1 thymidine kinase (see GenBank Acession X01712 J0225). Kit *et al.* teach gene encoding Herpes Simplex Virus Type 2 thymidine kinase (see GenBank Acession X03764). Drake *et al.* teach the nucleoside analog ganciclovir and AZT (see abstract); Waldman *et al.* teach the nucleoside analog acyclovir (see abstract); and Munch-Petersen *et al.* teach the nucleoside analog dideoxycytidine (see abstract).

Balasubramaniam *et al.* teach a multiple alignment of the amino acid sequences of 12 herpesviral deoxythiymidine kinases which shows that a conserved glutamine (Q) residue at position 127 (see entire publication and Fig. 1). Balasubramaniam *et al.* further teach that the most conserved site in the herpesviral deoxythiymidine kinases consists of the DRH motif which is involved in thymine recognition (see ***(iii) Sites 3 and 4***, p. 2981). Brown *et al.* teach that the region consisting of residues 161-192, which contains both the conserved glutamine residue at

position 127 and the DRH motif taught by Balasubramaniam *et al.*, is implicated in nucleoside binding (see **Nucleoside binding**, p. 878-879). Donarian *et al.* teaches and reviews the methods for the genetic deliver of enzymes for cancer therapy (see entire publication).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make an isolated nucleic acid according to claims 1-11 by modifying teachings of Munir *et al.* in the following manner: using the gene encoding Herpes Simplex Virus Type 1 thymidine kinase (taught by Graham *et al.*) or the gene encoding Herpes Simplex Virus Type 2 thymidine kinase (taught by Kit *et al.*), mutate at least one amino acid residue (i.e. substitution, insertion, or deletion of an amino acid residue) in the region encoding the Q substrate binding domain or the DRH binding domain or both domains by deleting, inserting, or substituting nucleotide(s) using methods taught by Munir *et al.* or other methods well known in the art such as treatment with chemical mutagens or site-directed mutagenesis in order to produce one or more mutations; insert mutant DNAs into expression vectors; transform host cells; and screen for mutants having the desired properties such as at least a one-fold increase in enzyme activity compared to wild-type thymidine kinase or increased ratio of the rate of phosphorylation of nucleoside analog substrates (such as ganciclovir, acyclovir, AZT, and dideoxycytidine) by mutant thymidine kinase to the rate of phosphorylation of nucleoside analog substrates by wild-type thymidine kinase (*cf.* claims 9 and 10).

One of ordinary skill in the art would be motivated to make an isolated nucleic acid according to claims 1-11 because Balasubramaniam *et al.* and Brown *et al.* teach that the Q substrate binding domain and the DRH binding domain are important in nucleoside binding and that in order to obtain mutants having the desired properties (i.e. increased enzyme activity or greater substrate/analog/prodrug specificity) this region must be modified. Furthermore, thymidine kinase mutants having increased activity toward prodrugs such as ganciclovir are expected to be more effective in the treatment of cancer when these mutants are used in gene therapy as taught by Donarian *et al.*

4. Claims 12-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Esandi *et al.* in view of Munir *et al.*, Graham *et al.*, Kit *et al.*, and Donarian *et al.*

Esandi *et al.* teach a vector containing the cytomegalovirus immediate early promoter and the herpes simplex thymidine kinase gene; gene therapy of experimental malignant mesothelioma using this vector; and potential use of this gene therapy as a local treatment for malignant mesothelioma (see abstract and entire publication). Esandi *et al.* do not teach the expression vector of claims 12-15. The teachings of Munir *et al.*, Graham *et al.*, and Kit *et al.* have been stated above. Donarian *et al.* further teach that the αfetoprotein promoter (a tissue specific promoter) is suitable in the control of prodrug activating or toxic enzymes in the gene

therapy of cancer (see **Table 2**, p. 237 and entire publication).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make an expression vector according to claims 12-15 by modifying the teachings of Esandi *et al.* by inserting the mutated DNA encoding mutant thymidine kinase described above in the rejection of claims 1-11 into the expression vector taught by Esandi *et al.* by methods well known in the art. Alternatively, the expression vector taught by Esandi *et al.* is modified by replacing the cytomegalovirus immediate early promoter with well known mammalian expression promoters (MoMLV LTR or cytomegalovirus immediate early promoter) or the tissue specific α fetoprotein promoter taught by Donarian *et al.* using methods well known in the art; and the mutated DNA encoding thymidine kinase described above in the rejection of claims 1-11 is inserted into this modified vector. One of ordinary skill in the art would be motivated to make an expression vector according to claims 12-15 in order to express thymidine kinase mutants in cancer cells of specific tissue origin which is expected to be effective in the treatment of cancer when these mutants are used in gene therapy as taught by Donarian *et al.*

Conclusion

5.. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christian L. Fronda whose telephone number is (703)305-1252. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, can be reached at (703)308-3804. The fax phone number for this Group is (703)308-0294. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1600 receptionist whose telephone number is (703)308-0196.

CLF
June 28, 2000

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